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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RAYMOND P. WARRELL, ROBERT E. KLEM,
and HOWARD FINGERT

Appeal 2009-010167
Application 09/709,170
Technology Center 1600

Decided: February 16, 2010

Before TONI R. SCHEINER, ERIC GRIMES, and STEPHEN WALSH, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating cancer. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

STATEMENT OF THE CASE

The Specification discloses that "[i]n many types of human cancers, a gene termed bcl-2 (B cell lymphoma/leukemia-2) is overexpressed, and this overexpression may be associated with tumorigenicity" (Spec. 1). The Specification discloses that "bcl-2 antisense oligomers, when administered to patients at high doses for a short period of time, *i.e.,* less than 14 days, … resulted in significant therapeutic responses in the treatment of cancer patients. These therapeutic regimens further encompassed administering the bcl-2 antisense oligomer at high doses for the short time in combination with one or more cancer therapeutics." (Spec. 4).

Claims 1, 3-5, and 7-23 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method of treating cancer in a human comprising administering to said human, in which such treatment is desired, a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day in more than one cycle of therapy, each cycle of therapy consisting of 3 to 9 days, wherein each cycle of therapy is separated by an interval of time wherein said human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day, and further comprising administering one or more cancer therapeutics.

OBVIOUSNESS

Issue

The Examiner has rejected claims 1, 3-5, and 7-23 under 35 U.S.C. § 103(a) as being obvious in view of Webb,[1] Waters,[2] and Bennett.[3]

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[1] A. Webb et al., "*BCL-2 antisense therapy in patients with non-Hodgkin's lymphoma*," 349 THE LANCET 1137-1141 (1997)

The Examiner finds that Webb discloses "bcl-2 antisense therapy at a dose from 4.6 mg/m^2 to 73.6 mg/m^2 in human patients with non-Hodgkin lymphoma" (Ans. 4), and that a 14 day course of therapy resulted in an "improvement in symptoms and tumor shrinkage" in two patients (*id.*). The Examiner finds that Waters discloses bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma using repeated courses of treatment and in combination with other therapeutic agents (*id.* at 5).

The Examiner finds that Bennett discloses treatment of cancer using bcl-x (a family member of bcl-2) antisense oligonucleotides and chemotherapeutics (*id.* at 5). The Examiner finds that Bennett discloses that the optimization of treatment schedules is within the skill of one in the art and that treatment times may vary from several days to several months (*id.* at 5-6). The Examiner concludes that "[o]ne of ordinary skill in the art would have been motivated to administer the antisense in a cycle of therapy comprising 3 to 9 days since Bennett et al. taught that dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months" (*id.* at 7).

Appellants contend that the "none of the cited art provides the claim elements of 'more than one cycle of therapy,' '3 to 9 days,' and 'separated by an interval of time wherein no bcl-2 antisense oligonucleotide is administered'" (Appeal Br. 10). Appellants also contend that, in the absence of impermissible hindsight, the cited references would not have suggested

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[2] Justin S. Waters et al., "*Phase I Clinical and Pharmacokinetic Study of Bcl-2 Antisense Oligonucleotide Therapy in Patients With Non-Hodgkin's Lymphoma*," 18 JOURNAL OF CLINICAL ONCOLOGY 1812-1823 (2000)

[3] Bennett et al., US 6,214,986 B1, Apr. 10, 2001

the cycle of therapy required by the claims (*id.*) and would not have provided a reasonable expectation of success (Reply Br. 9).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the cited references would have made obvious the method of claim 1 with repeated 3- to 9-day cycles of therapy separated by a day of nontreatment?

Findings of Fact

1. Webb discloses that a *bcl-2* "antisense oligonucleotide was administered for 2 weeks to nine patients who had BCL-2-positive relapsed non-Hodgkin lymphoma" (Webb 1137).

2. Webb discloses that "[d]uring the course of the study, the daily dose of *BCL-2* antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2" (*id.*).

3. Webb discloses that

> [i]n two patients, computed tomography scans showed a reduction in tumour size (one minor, one complete response). In two patients, the number of circulating lymphoma cells decreased during treatment. In four patients, serum concentrations of lactate dehydrogenase fell, and in two of these patients symptoms improved. We were able to measure BCL-2 levels by flow cytometry in the samples of five patients, two of whom had reduced levels of BCL-2 protein.

(*Id.* at 1137.)

4. Webb discloses that a two-week treatment was given and that a second course was considered if there was evidence of tumor response (*id.* at 1138).

5. Webb discloses that patient 1 was given two courses of treatment (*id.* at 1139).

6. Webb discloses that "six of eight patients who were treated with chemotherapy after antisense treatment went on to achieve a partial remission" (*id.* at 1140).

7. Waters discloses treating patients with non-Hodgkin's lymphoma with "a 14-day subcutaneous infusion of G3139, an … oligonucleotide complementary to … the *bcl-2* open reading frame" (Waters 1812).

8. Waters discloses that the "patients were treated at doses ranging from 4.6 mg/m^2/d to 195.8 mg/m^2/d" (*id.* at 1813).

9. Waters discloses that the "only hematologic toxicity that seemed to be unequivocally related to G3139 therapy was thrombocytopenia (Table 2). … In all of these cases, the platelet count fell progressively during the course of the G3139 infusion and recovered after discontinuation of treatment." (*Id.* at 1813.)

10. Waters discloses that

> [a]lthough this was primarily a safety study, there was evidence for clinical antitumor activity and for specific downregulation of Bcl-2 protein in target tissues. Three patients with low-grade lymphoma had an objective reduction in overall tumor bulk after treatment, and one of them had a complete remission that has been sustained for 36 months.

(*Id.* at 1819.)

11. Waters discloses that "[o]ne course of treatment was planned per patient, but additional courses of treatment were considered in the event of a tumor response. A second course was administered to patients no. 2, 17, and 21." (*Id.* at 1813.)

12. Waters discloses that there "is great potential for the further development of *bcl-2* antisense oligonucleotides in the treatment of malignant disease. One of the most interesting possibilities is their use as

chemosensitizing agents … [in] malignancies characterized by Bcl-2 overexpression." (*Id.* at 1821.)

13. Bennett discloses "[a]ntisense compounds … targeted to nucleic acids encoding bcl-x.... Methods of using these compounds for modulation of bcl-x expression and for treatment of diseases associated with expression of bcl-x are also provided." (Bennett, abstract)

14. Bennett discloses that the

> formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved.… Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates.

(*Id.* at col. 16, l. 59 to col. 17, l. 2.)

15. Appellants have provided a declaration under 37 C.F.R. § 1.132 of Steven Craig Novick (filed July 16, 2007, Appeal Br. 21).

16. Dr. Novick states that the

> results reported in Webb and Waters are not impressive, and therefore, one skilled in the art reviewing these references would not be motivated to provide a shorter course of therapy, especially since most of [sic] all of the patients in the studies did not respond satisfactorily, despite 14 days of treatment. Those skilled in the art that develop drugs and treatment regimens do not routinely shorten cycles of therapy. To be motivated to do so (and to go against accepted treatment schedules) would require convincing results, which simply are not reported in Webb and Waters.

(Novick Declaration, ¶ 9.)

Principles of Law

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).

The obviousness "analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

"It is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

"Obviousness does not require absolute predictability of success.... For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

"[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter-Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

Analysis

Claim 1 is directed to a method of treating cancer comprising administering a bcl-2 antisense oligonucleotide in more than one cycle of therapy, each lasting 3 to 9 days and separated by at least one day. (Claim 1 also requires a particular range of antisense dosages and administration of an

additional cancer therapeutic, but Appellants do not dispute that the prior art would have made obvious those limitations.)

Webb and Waters both disclose treatment of cancer by administering bcl-2 antisense oligonucleotides for a 14-day cycle, and disclose repeated cycles of treatment. Bennett also discloses the treatment of human cancer with antisense oligonucleotides and states that a person of ordinary skill in the art "can easily determine optimum dosages, dosing methodologies and repetition rates" for such treatments. Bennett also discloses that the course of treatment may last from several days to several months.

In view of these disclosures, it would have been obvious to one of skill in the art to modify the prior art 14-day bcl-2 antisense oligonucleotide treatment cycle to provide repeated 3- to 9-day cycles of treatment. Such a modification is disclosed by Bennett to be a variable for which optimization is routine and well within the skill of those in the art. A person of ordinary skill in the art would reasonably expect that, for example, two 7-day cycles of treatment, separated by one day of nontreatment, would provide a similar therapeutic effect as the 14-day treatments disclosed by Webb and Waters.

Appellants argue that the cited references do not suggest repeated 3- to 9-day cycles of therapy (Appeal Br. 13). Appellants argue that "[a]t most, one would obtain the generally accepted 14-day bcl-2 ASO [antisense oligonucleotides] treatment cycle (as taught by Webb) perhaps followed by a second generally accepted 14-day bcl-2 ASO treatment cycle (as taught by Waters), perhaps further comprising one or more cancer therapeutics (as taught by Bennett)" (*id.* at 21). Appellants argue that the Novick Declaration establishes "that one skilled in the art would not have shortened the 14-day cycle in Webb, regardless of reduced bcl-2 levels in Webb or

Bennett's boilerplate language regarding optimal dosing of ASOs. Rather, the skilled artisan would have continued with longer courses of therapy given the overall unsatisfactory results provided in Webb and Waters." (*Id.*)

This argument is not persuasive. First, claim 1 does not require shortening the overall period of treatment from that taught by the prior art. The claim encompasses fourteen days of ASO treatment; it just requires that the fourteen days be split into two seven-day treatments, separated by a day of nontreatment. As discussed above, a person of ordinary skill in the art would reasonably expect the two treatment regimens to provide similar results.

In addition, Bennett discloses that treatment protocols with antisense oligonucleotides and chemotherapeutic agents would be routinely optimized by one of skill in the art. One of skill in the art would reasonably expect that the optimal treatment protocol when using a combination of antisense oligonucleotides and chemotherapeutics would differ from the optimal protocol when administering antisense oligonucleotides alone, as taught by Webb and Waters, and therefore it would have been obvious to optimize the combination therapy suggested by the references.

Appellants also contend that the Examiner erred in finding that the references provide a reasonable expectation of success (Reply Br. 9). Appellants argue that "[n]o showing has been made that reducing the time of administration below 14 days (in particular the claimed 3-9 days) would be efficacious in the treatment of cancer" (*id.*).

This argument is not persuasive. In accord with *In re O'Farrell*, obviousness only requires a reasonable expectation of success, but not an absolute predictability of success. As discussed above, claim 1 does not

require shortening the overall length of treatment from that taught by the references, only splitting a continuous fourteen-day treatment into, for example, two seven-day treatments separated by a day of nontreatment. Appellants have not provided evidence showing that a skilled worker would have expected a single day of nontreatment to interfere with the therapeutic efficacy of Webb's or Waters' treatment.

Appellants contend that the "invention is based, in part, on the discovery that short treatment cycles and/or high doses of bcl-2 ASO, alone or in combination with other therapeutic agents, unexpectedly provides greater ameliorative effects with less toxicity in human patients suffering from cancer compared to previous treatment regimens." (Appeal Br. 13).

This argument is not persuasive. In accord with *In re Baxter-Travenol Labs.,* unexpected results must be shown in comparison to the closest prior art. Here, Appellants have pointed to no evidence of record that provides a comparison of the method of claim 1 with the treatment methods disclosed in the prior art. Therefore, the record does not establish that the claimed method is unexpectedly superior to the methods taught by the closest prior art.

With regard to claim 5, Appellants argue that claim 5 is nonobvious "for the *additional reason* that Waters, which enlarged the study of Webb, clearly states that the maximum tolerated does of bcl-2 ASO was 4.1 mg/kg/day. *See* page 1815." (Appeal Br. 24.)

Claim 5 depends on claim 1 and further requires administering 5 to 7 mg/kg/day of bcl-2 antisense oligonucleotide. Waters discloses that "DLTs [dose-limiting toxicities] were observed in patients treated at doses of 147.2 $mg/m^2/d$ and above.... The maximum-tolerated dose was therefore

considered to be 147.2 mg/m^2/d (approximately 4.1 mg/kg/d)." (Waters 1815, right col.)

The Examiner did not respond in the Answer to Appellants' argument with respect to claim 5. We agree with Appellants that Bennett's general direction to optimize dosages, when viewed in light of Waters' disclosure that the maximum-tolerated dose of a bcl-2 antisense oligonucleotide was 4.1 mg/kg/d, would not have led a person of ordinary skill in the art to the dosage range recited in claim 5. We therefore reverse the rejection of claim 5.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the cited references would have made obvious the method of claim 1 with repeated 3- to 9-day cycles of therapy separated by a day of nontreatment. But the evidence does not support the Examiner's conclusion that the cited references would have suggested the dosage range recited in claim 5.

SUMMARY

We affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as being obvious in view of Webb, Waters, and Bennett. Claims 3, 4, and 7-23 fall with claim 1 because they were not argued separately. 37 C.F.R. § 41.37(c)(1)(vii). We reverse the rejection of claim 5.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

lp

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